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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/925,720	GIGUERE ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *1-14,22-27,32-34 and 39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-21,28-31 and 35-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3-7&8-5-02*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

It is readily apparent from the restriction that Group II is directed toward a method of screening compounds using transgenic non-human animals as in claims 15-21, 28-31 and 35-38. Therefore, it is readily apparent that claims 1-14 were inadvertently included in Group II because of a typographical error.

Applicant's election of Group II, claims 1-21, 28-31 and 35-38, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). It is readily apparent from the restriction that Group II is directed toward a method of screening compounds using transgenic non-human animals as in claims 15-21, 28-31 and 35-38. Therefore, it is readily apparent that claims 1-14 were inadvertently included in Group II because of a typographical error.

Claims 1-14, 22-27, 32-34 and 39 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

Claims 15-21, 28-31 and 35-38 are under consideration in the instant office action.

Sequence Listing

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37

CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. **The sequence on pg 13, line 11, pg 14, line 17, and pg 17, line 3, and in claims 23 and 33 needs a SEQ ID NO. The sequence listing may not include the sequence, which would require a new CRF and paper copy of the sequence listing.** Applicants must file a "Sequence Listing" accompanied by directions to enter the listing into the specification as an amendment. Applicant also must provide statements regarding sameness and new matter with regards to the CRF and the "Sequence Listing." Applicant is requested to return a copy of the attached Notice to Comply with the reply. Failure to fully comply with the sequence rules in response to the instant office action will be considered non-responsive.

Specification

The specification is objected to because the first line of the specification should state the application claims priority to US Provisional Application No: 60/119,024, filed 2-8-99.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 15-21, 28-31 and 35-38 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility.

Claims 15-21, 28-31 and 35-38 are directed toward a method of screening compounds using a non-human transgenic animal, specifically a mouse, having a disruption of the endogenous ERRα orphan nuclear receptor having an altered fat metabolism and/or glucose metabolism as compared to a control animal. The specification teaches making ERRα -/- mice (Example 2, pg 38; Example 4, pg 40, line 11). The ERRα -/- mice had decreased body mass, lower body fat (¶ bridging pg 40-41), a decreased intestinal capacity for fatty acid esterification (pg 43, lines 6-9), normal core temperature, basal metabolic rate and expression levels of uncoupling protein (pg 44, lines 14-17). The mice were treated with 3H2O and showed decreased lipidogenesis as compared to littermate controls (pg 45, lines 9-10). The specification does not teach how to use the mice to screen and identify compounds that modulate EERα receptor activity. Compounds that modulate ERRα activity cannot be found using the animals of claims 1-5 as claimed because the mice of claims 1-5 have a disruption of ERRα; ERRα activity cannot be assayed in mice that do not express ERRα. The method claimed does not have a use because the mouse described in the specification does not have a use; the phenotype described in the specification does not correlate to a disease state linked to a disruption in ERRα. The specification suggests using the mice as a model of disease (pg 3, lines 10-15), specifically as a model of obesity. However, the mice described in the specification are not obese and the

specification does not disclose ERRα disruptions are linked to obesity in humans. None of the phenotypes described correlate to a useful phenotype because the phenotypes are not specific to a disease and are not linked to a disruption in the ERRα gene in humans. Using the mice to determine whether a particular feature of the ERRα -/- mice is ameliorated is not a specific or substantial utility because the specification does not link the phenotype to any specific disease or to a disease caused by a disruption in humans. The specification does not identify any compounds that change any phenotype found ERRα -/- mice. Finally, the ligand for ERRα is unknown (Chen, 2001, J. Biological Chem., Vol. 276, No. 30, pg 28465-28470). Thus, the specification does not provide a specific or substantial use for a mouse as claimed, specifically having altered fat and/or glucose metabolism as claimed.

Claims 15-21, 28-31 and 35-38 encompass using non-human animals having a disruption of endogenous ERRα and an insertion of a non-endogenous ERRα gene. Applicants do not teach such animals have a normal phenotype or that such mice provide any use over wild-type animals. Applicants do not teach such an animal or using the animal to identify any compounds that modulate ERRα activity. Therefore, methods of screening compounds using animals having a disruption of endogenous ERRα and an insertion of non-endogenous ERRα do not have a specific or substantial use because the methods can be performed in wild-type animals.

Claim 31 encompasses using a transgenic human, which is non-statutory subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-21, 28-31 and 35-38 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use mice having a disruption in the ERRα gene as claimed.

The specification does not teach how to make animals or cells having a disruption in the ERRα gene other than mice. The only means of making a non-human animal with a disruption in the ERRα gene taught in the specification is by using mouse embryonic stem cell technology. The state of the art at the time of filing was such that embryonic stem (ES) cell technology had only been successful in mice. Wagner (May 1995, Clin. and Experimental Hypertension, Vol. 17, pages 593-605) and Mullins (1996, J. Clin. Invest., Vol. 98, pages S37-S40) taught germline transmission of ES cells has not been demonstrated in species other than mice and the growth of ES cells from species other than mice is unreliable. Wall (1996, Theriogenology, Vol. 45, pg 57-68) taught transgene expression and the physiological result of such expression in livestock was not always accurately predicted in transgenic mice (page 62, line 7). Since the time of filing, Zan (Nature Biotech, 2003, Vol. 21, pg 645-651) taught making knockout

rats using mutagenized male rats, which was not taught in the specification and considered essential to making knockout rats. The specification fails to provide sufficient guidance to make transgenics other than mice by teaching obtaining ES cells in species other than mice. The specification does not teach the nucleic acid sequence of the ERRα gene in non-mice, non-human species or correlate the ERRα gene in mice to the ERRα gene in other species. The specification does not teach how to make knockout animals other than mice or correlate making knockout mice to other species. Therefore, the specification does not provide adequate guidance for one of skill in the art to make a transgenic, non-human animal or cells having a disruption in the ERRα gene in any species other than mice.

The specification does not provide adequate correlation between the phenotype obtained in mice to the phenotype obtained in other species. The state of the art at the time of filing was that the phenotype of transgenic mice does not predict the phenotype in non-mice species. Models of human diseases have relied on transgenic rats when the development of transgenic mice having the desired phenotype was not feasible. Mullins (1990, Nature, Vol. 344, pg 541-544) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse Ren-2 renin transgene. Hammer (1990, Cell, Vol. 63, pg 1099-1112) describes spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human b_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice (Mullins, 1989, EMBO, Vol. 8, pg 4065-4072; Taurog, 1988, J.

Immunol., Vol. 141, pg 4020-4023) expressing the same transgenes that successfully caused the desired symptoms in transgenic rats. Therefore, the specification does not enable making transgenic having the disclosed phenotypes in species other than mice.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15-21 28-31 and 35-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It cannot be determined how compounds that modulate ERRα activity can be found using the mice of claim 5 as in claim 15 because the mice do not have an endogenous ERRα gene. The method used to "determine" whether a compound increases or decreases ERRα activity in step b) of claim 15 cannot be determined.

The mice described in the specification have normal body temperature, basal metabolism and uncoupling protein expression; therefore, it is unclear how to use such parameters as in claim 16 to determine whether a compound increases or decreases ERRα activity.

The metes and bounds of "hepatic synthetic functions" in claim 16 cannot be determined. The phrase is not defined in the specification and does not have an art recognized meaning.

The metes and bounds of "compounds suspected of being a modulator of ERRα" in claim 17 cannot be determined. It is unclear if any compound is encompassed by the phrase or if the compounds must meet certain criteria before being used in the method.

It cannot be determined how compounds that modulate ERRα activity can be found using the mice of claim 5 as in claim 18 because the mice do not have an endogenous ERRα gene.

The metes and bounds of a "promoter... ...being modulated by ERRα" in claim 18 cannot be determined. It is unclear if the phrase is limited to promoters capable of being modulated by ERRα protein or if the phrase is limited to promoters that has been modulated by ERRα protein. The metes and bounds of promoters encompassed by either interpretation cannot be determined because the specification does not define such promoters or provide an assay for determining such promoters. Nor were such promoters taught in the art at the time of filing.

The "measuring" step of claim 18 is wholly unclear. It cannot be determined what is being measured or selected; i.e. the marker gene or the marker protein, what conditions are required, i.e. the presence or absence of an agent, or how to identify agents that modulate ERRα activity by comparing the marker in the presence or absence of the agent.

The metes and bounds of "agents suspected of modulating the promoter modulating activity of ERRα" in claim 18 cannot be determined. It is unclear if any compound is encompassed by the phrase or if the compounds must meet certain

criteria before being used in the method. In addition, the promoter modulating activity of ERRα is unclear as it is not discussed in the specification.

The metes and bounds of "ERRα or related factors" in claim 28 is unclear. How related must the factor be to ERRα to be within the metes and bounds of the claim?

Step a) in claim 28 is unclear. The phrase "which modulates activity thereof by an interaction thereto of said ERRα and related factors" is unclear because it is unclear to what "thereof" and "thereto" refers, i.e. ERRα or related factors vs. the promoter. The structure of the products required in step a) are not clearly set forth.

The phrase "said transcriptional activity" in claim 28, step b) does not have antecedent basis in step a) which only requires "a transcriptionally active preparation of ERRα".

The phrase "or of a binding of at least ERRα or related factors to said cis-acting sequence..." in step b of claim 28 does not make sense. The alternative condition cannot be determined.

The first "measuring" step of claim 28 is wholly unclear. It cannot be determined what is being measured or selected; i.e. the activity of the promoter or of ERRα, what conditions are required, i.e. the presence or absence of an agent, or how to identify agents that modulate ERRα activity by comparing the "activities" in the presence or absence of the agent.

The metes and bounds of "agents suspected of modulating the transcriptional activity of ERRα" in claim 28 cannot be determined. It is unclear if any compound is encompassed by the phrase or if the compounds must meet certain criteria before being

used in the method. In addition, the transcriptional activity of ERRα is unclear as it is not discussed in the specification.

The second "measuring" step of claim 28 is wholly unclear. The phrase "and comparing same with that of a control animal, not having been administered" is unclear because it cannot be determined what is the "same." It cannot be determined how to identify agents that modulate ERRα activity by comparing the fat tissue growth or weight gain of an ERRα -/- mouse given the agent with the fat tissue growth or weight gain of an ERRα -/- mouse not given the agent because ERRα -/- mice do not express ERRα. It cannot be determined how to identify agents that modulate ERRα by comparing the fat tissue growth or weight gain of an ERRα -/- mouse given the agent with the fat tissue growth or weight gain of a wild-type mouse given the agent because all wild-type mice are have higher fat tissue growth and weight gain as compared to ERRα -/- mice.

Claim 28 requires using a non-human animal. Dependent claim 30 requires the animal is a mammal. However, dependent claim 31 states the mammal is a human, which is excluded in parent claim 28. Human should be deleted from claim 31.

The metes and bounds of "ERRα or related factors" in claim 35 is unclear. How related must the factor be to ERRα to be within the metes and bounds of the claim?

Step a) in claim 35 is unclear. The phrase "which modulates activity thereof by an interaction thereto of said ERRα and related factors" is unclear because it is unclear to what "thereof" and "thereto" refers, i.e. ERRα or related factors vs. the promoter. The structure of the products required in step a) are not clearly set forth.

The phrase "said transcriptional activity" in claim 35, step b) does not have antecedent basis in step a) which only requires "a transcriptionally active preparation of ERRα".

The phrase "or of a binding of at least ERRα or related factors to said cis-acting sequence..." in step b of claim 35 does not make sense. The alternative condition cannot be determined.

The "measuring" step of claim 35 is wholly unclear. It cannot be determined what is being measured or selected; i.e. the activity of the promoter or of ERRα, what conditions are required, i.e. the presence or absence of an agent, or how to identify agents that modulate ERRα activity by comparing the "activities" in the presence or absence of the agent.

The metes and bounds of "agents suspected of modulating the transcriptional activity of ERRα" in step b of claim 35 cannot be determined. It is unclear if any compound is encompassed by the phrase or if the compounds must meet certain criteria before being used in the method. In addition, the transcriptional activity of ERRα is unclear as it is not discussed in the specification.

The "assessing" step of claim 35 is wholly unclear. The phrase "and comparing same with that of a control animal, not having been administered" is unclear because it cannot be determined what is the "same." It cannot be determined how to identify agents that modulate ERRα activity by comparing the obesity of an ERRα -/- mouse given the agent with the obesity of an ERRα -/- mouse not given the agent because the mice do not express ERRα. It cannot be determined how to identify agents that

modulate ERRα by comparing the obesity of an ERRα -/- mouse given the agent with the obesity of a wild-type mouse given the agent because all wild-type mice are obese as compared to ERRα -/- mice.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120. The examiner's phone number will change on Jan. 12th, 2004 to 571-272-0738.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER